

Novartis Institutes for BioMedical Research

SAF312

Clinical Trial Protocol CSAF312X2201

A randomized, vehicle-controlled, subject and investigator-masked, proof-of-concept study to evaluate the use of topical ocular SAF312 in the treatment of postoperative ocular pain in patients undergoing photorefractive keratectomy (PRK) surgery

Document type:	Amended Protocol Version
EUDRACT number:	N/A
Version number:	v02 (Clean)
Clinical Trial Phase:	Phase II
Release date:	11-Apr-2017

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to [Section 9.2](#) of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Drug Safety and Epidemiology (DS&E) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

AE	adverse event
AK	anterior keratectomy
b.i.d.	twice a day
BMI	Body Mass Index
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ePRO	electronic Patient Reported Outcomes
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
OPAS	Ocular Pain Assessment Survey
OU	Both eyes (study eye and fellow eye)
PD	pharmacodynamic(s)

PK	pharmacokinetic(s)
PRK	photorefractive keratectomy
SAE	serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SE	Study eye
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d.	three times a day
VAS	Visual analog scale
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUC _{0-t}	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC _{inf}	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUC _{last}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUC _{tau}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUC _{tau,ss}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
C _{last}	The last observed quantifiable concentration [mass / volume]
C _{max}	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
C _{min}	The lowest concentration observed during a dosing interval. C _{min} can occur at 0 hours (pre-dose) or at the end of a lag-phase or at the end of the dosing interval if no lag-phase exists. [mass / volume]
C _{min,ss}	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
R _{acc}	The accumulation ratio
T _{1/2}	The terminal elimination half-life [time]
T _{last}	The time point that corresponds to the last measurable concentration [time]
T _{max}	The time to reach the maximum concentration after drug administration [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest

Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of
consent (WoC)

Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Corporate Confidential Information

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Protocol synopsis

Protocol number	CSAF312X2201
Title	A randomized, vehicle-controlled, subject and investigator-masked, proof-of-concept study to evaluate the use of topical ocular SAF312 in the treatment of postoperative ocular pain in patients undergoing photorefractive keratectomy (PRK) surgery
Brief title	Study of SAF312 as an eye drop for treatment of eye pain following photorefractive keratectomy (PRK) surgery
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine if SAF312 eye drops four times daily has an adequate safety and efficacy profile to justify further clinical development for the treatment of ocular pain associated with corneal epithelial defect such as after PRK surgery
Primary Objective(s)	To evaluate pain control in the immediate post-operative period.
Secondary Objectives	To evaluate the efficacy of SAF312 eye drops for reducing use of oral analgesics following PRK procedure. To assess safety and tolerability of SAF312 eye drops four times daily. To evaluate pain severity post-operatively. To assess the systemic exposure after ocular dosing of SAF312 eye drops four times daily at various time points in PRK patients.
Study design	This is a proof-of-concept, subject and investigator-masked, randomized, vehicle controlled study of SAF312 administered as eye drops in addition to standard of care treatment in patients after photorefractive keratectomy (PRK) surgery. Patients will be randomized to two sequences: 1) SAF312, followed by placebo, or 2) placebo, followed by SAF312. Each patient will receive the assigned dose four times daily for 72 hours following PRK surgery on their study eye (Day 1, Periods 1 and 2). The initial study eye will be the non-dominant eye as established at screening and in agreement of the patient and the PI. Each patient will return for follow-up visits on Days 2, 3, 4 and 8 after surgery of Periods 1 and 2.
Population	Approximately 40 male and female patients who are eligible for PRK surgery and between 18 and 75 years old (inclusive).
Key Inclusion criteria	<ul style="list-style-type: none"> Male and female patients age 18 to 75 who are eligible for bilateral PRK surgery. Normal eye exam except for refractive error at baseline. Planned myopia correction should not exceed -4.00 Diopters (sphere) and 3.00 diopters of astigmatism, with spherical equivalent not higher than -4.50, confirmed by manifest refraction at baseline. Monovision treatment is allowed.

Key Exclusion criteria	<ul style="list-style-type: none"> • Monocular patient (including amblyopia) or best corrected visual acuity score worse than 20/80 (Snellen), or 55 letters (EDTRS), at baseline. • Any systemic or ocular disease that might affect wound healing (such as severe rheumatoid arthritis or diabetes or history of keloid formation) or a history of ocular trauma, uveitis, infection, or inflammation in the 6 months prior to baseline. Patients with mild, well controlled diabetes with no evidence of ocular or systemic complications of diabetes can be included. • Patients with active inflammatory or infectious ocular conditions, severe or progressive retinal disease, and use of topical or systemic steroids, or use of coumadin or similar drugs within the last 6 months prior to baseline. • Patients with any corneal dystrophy (epithelial, stromal or endothelial) or any cornea disease (including significant scarring, ocular herpes or pterygium). • Previous refractive or corneal surgery (such as LASIK, PRK, radial keratotomy, pterygium removal, corneal transplantation). • History of allergic or hypersensitivity reaction or significant adverse events to any of the drugs to be used in this study including: <ul style="list-style-type: none"> • tetracaine or similar topical ocular anesthetic • NSAIDs and aspirin • oral analgesic (including acetaminophen and codeine) • antibiotics • steroids • inability to tolerate or wear bandage contact lens • Chronic pain of any etiology or any significant illness which has not resolved within two (2) weeks prior to initial dosing. • Concurrent therapy or history of chronic therapy or abuse of systemic or ocular NSAIDs, analgesics, pain medication (including gabapentin or pregabalin and similar), opiates or cannabis. Patients with use of any topical eye medication except for lubricating eye drops within two weeks prior to surgery, in the study eye will be excluded. Patients with any use of topical or systemic NSAIDs during the 30 days before the study, or use of Restasis® within the 3 months prior to surgery will also be excluded. • History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing. Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days." • Subjects using CPAP or other sleep apnea devices. • Subjects who do not weigh at least 50 kg, or who do not have a body mass index (BMI) within the range of 18 - 35 kg/m². BMI = Body weight (kg) / [Height (m)]² • Pregnant or nursing (lactating) women.
Study treatment	SAF312 and placebo, multiple topically delivered doses
Efficacy/PD assessments	<p>Visual Analog Scale (VAS) for pain</p> <ul style="list-style-type: none"> • Incidence of and amount (mg/kg of body weight) of rescue oral analgesics needed in each treatment period

Key safety assessments	<ul style="list-style-type: none"> • Adverse event monitoring - AEs and SAEs • Vital sign monitoring (blood pressure, pulse rate, and body temperature) • Ocular exam and assessment results <ul style="list-style-type: none"> • Epithelial defects • Tear production • Blink rate • Size of epithelial defect by slit lamp exam • Ocular hyperemia • Dilated fundus exam • Intraocular pressure (IOP) • Visual acuity
Other assessments	Corporate Confidential Information
Data analysis	<p>The primary efficacy analysis will assess the effect of SAF312 eye drops on the pain visual analog scale (VAS) pain assessment prior to the 6 hour dose post-operatively compared to vehicle, and the average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment compared to vehicle. The secondary efficacy analysis will assess the effect of SAF312 eye drops on whether patients need oral analgesics in 24 hours, 2 days, and 3 days post-operatively compared to vehicle, as well as the amount of oral analgesics needed in 12 hours, 24 hours, 2 days, and 3 days post-operatively compared to vehicle.</p>
Key words	SAF312, proof-of-concept, efficacy, ocular pain, photorefractive keratectomy, PRK

1 Introduction

1.1 Background

SAF312, a potent inhibitor of the transient receptor potential cation channel subfamily V member 1 (TRPV1), is currently in development as topical ocular eye drops for the treatment of post-operative pain after photorefractive keratectomy (PRK).

In the oral administration program, SAF312 was evaluated in a total of four clinical studies (SAD, MAD, PoC for post-operative dental pain and PoC for neurogenic detrusor overactivity due to spinal cord lesions). The development of oral SAF312 did not progress because of dose-dependent inhibition of noxious heat pain perception.

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In the Proof of Concept study of SAF312 for postoperative pain after PRK the dose of 1 drop of SAF312 4 times daily for 3 days will be used, as this was estimated as the therapeutic dose and provides a margin of safety from the MTD that was at the same drug concentration but at 8 times daily for 7 days. Pain after PRK is currently partially treated with Non-Steroid-Anti-Inflammatory (NSAID) or diluted anesthetic ocular drops; both groups of drugs have the side effect of delaying wound healing.

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There is an unmet medical need for pain control using a topical ocular drug that does not delay wound healing.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the IB.

1.2 Nonclinical data

SAF312 is a selective, non-competitive, reversible inhibitor of TRPV1 channels. SAF312 inhibited capsaicin, low pH and anandamide stimulation of human TRPV1 with IC₅₀ values of 12, 5, and 10 nM, respectively. Characterization of the selectivity of SAF312 resulted in no activity of >50% inhibition at 10 µM being observed for a total of 278 GPCRs, transporters, ion channels, nuclear receptors and enzymes. SAF312 was highly selective versus other TRP channel family members and had no activity against estrogen receptors. SAF312 exhibits pharmacodynamic activity in acute and long lasting inflammatory hyperalgesia nonclinical models. SAF312 showed sustained analgesic properties upon repeated oral dosing. Recent evidence has indicated a link between TRPV1 inhibition and hyperthermia, and this

was confirmed for SAF312 in clinical studies. However, topical dosing in the eye will limit systemic effects of SAF312 while achieving inhibition of corneal TRPV1.

Accumulating data indicates a primary role for TRPV1 in ocular pain. TRPV1 is expressed in several corneal cell types in humans including the corneal epithelium, stroma and endothelium (Zhang et al 2007, Yang et al 2013a, Mergler et al 2010) and also has been localized to the ophthalmic branch of trigeminal nerve endings in the mouse cornea (Bates et al 2010). A role for TRPV1 in neurogenic pain in the cornea may be assumed given the co-localization of TRPV1 with substance P and calcitonin-gene-related peptide (CGRP) receptor in rat corneal neurons (Murata and Masuko 2006) and by the fact that TRPV1 agonists can trigger release of tachykinins (reviewed in Yang et al 2013b).

The role of TRPV1 in wound healing in the eye is complex. TRPV1 knockout mice were reported to have reduced corneal epithelial migration and proliferation following epithelial debridement (Sumioka et al 2014). However, homozygous TRPV1 knockout mice were reported to have reduced inflammation and fibrosis in a mouse corneal wound healing model (Okada et al 2011). Additionally, treatment with a TRPV1 agonist topically on the cornea, which ablated TRPV1-expressing corneal neurons, had an analgesic effect without damaging the cornea or impairing corneal wound healing in mice (Bates et al 2010), suggesting that loss of TRPV1 activity reduces pain sensation and does not affect wound healing. Moreover, TRPV1 activation by hypertonic stress in human corneal epithelial cells induced the release of inflammatory cytokines (Pan et al 2011). These studies clearly show a role for TRPV1 in corneal nociception and inflammatory responses in the cornea. Expression of TRPV1 has been confirmed in the human cornea epithelium and stroma and in corneal nerves.

Overall, there is a well-validated role for TRPV1 in corneal nociception. SAF312 is a potent antagonist of TRPV1 that achieves therapeutic levels in the cornea following topical administration. Unlike steroids or NSAIDs, topical treatment of SAF312 did not affect the rate of corneal wound healing. It is expected that topical ocular dosing of SAF312 will result in minimal systemic exposure, below that associated with heat perception and hyperthermia, while preferentially targeting TRPV1 in the corneal nerve to reduce postoperative pain associated with PRK.

1.3 Clinical data

1.3.1 Human safety and tolerability data

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The most frequent ocular adverse events in the SAF312 treated patients were corneal staining, hyperemia and mild anterior chamber inflammation, in levels similar to placebo (refer to Investigator's Brochure for details).

For **oral** SAF312,

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A total of 379 subjects Corporate Confidential Information
have been exposed to study medication (271 of those to SAF312).

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1.4 Study purpose

To determine if SAF312 eye drops four times daily has an adequate safety and efficacy profile to justify further clinical development for the treatment of ocular pain associated with corneal epithelial defect such as after PRK surgery.

2 Study objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
<ul style="list-style-type: none">To evaluate pain control in the immediate post-operative period.	<ul style="list-style-type: none">Visual analog scale (VAS) pre-dose pain assessment at 6 hours post-operativelyAverage ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour assessment

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
<ul style="list-style-type: none">To evaluate the efficacy of SAF312 eye drops four times daily for reducing use of oral analgesics following PRK procedure	<ul style="list-style-type: none">Incidence of and amount of rescue oral analgesics needed in 12 hours, 24 hours, 2 days, and 3 days post-operatively after each PRK surgery.
<ul style="list-style-type: none">To assess safety and tolerability of SAF312 eye drops four times daily	<ul style="list-style-type: none">AEs and SAEsVisual acuity, intraocular pressure (IOP), dilated fundus exam, ocular hyperemiaSize of epithelial defect by slit lamp examBlink rate, tear production,Vital signs (blood pressure, pulse rate, and body temperature)
<ul style="list-style-type: none">To evaluate pain severity post-operatively	<ul style="list-style-type: none">All VAS measurements during the first 3 days after surgery
<ul style="list-style-type: none">To assess the systemic exposure after ocular dosing of SAF312 eye drops four times daily at various time points in PRK patients	<ul style="list-style-type: none">Plasma concentration of SAF312

3 Investigational plan

3.1 Study design

This is a proof-of-concept, subject and investigator-masked, randomized, vehicle controlled study of SAF312 administered as eye drops in addition to standard of care treatment in patients after photorefractive keratectomy (PRK) surgery. PRK surgery is performed as an outpatient procedure under topical anesthesia with removal of the corneal epithelium to expose the stroma for the laser ablation, as described in the SOM. SAF312 dosing will be as single eye drop of suspension C , administered four times daily (every six hours) in one eye from immediate post-op (time 0) to last dose at 72 hours.

Each patient, if eligible, will participate in this 2 treatment period, cross over study. Patients will undergo PRK surgery on 2 separate occasions (periods), one eye at a time. Patients will be randomized to receive SAF312 or vehicle following procedure 1 and the alternate following procedure 2 ([Figure 3-1](#)). Patients and investigator site staff will remain masked to treatment. Sponsor staff will be unmasked for evaluation of adverse events and for interim analysis, as detailed in [Section 6.4](#).

SAF312 has been shown to be safe in humans with intact corneas (CSAF312X2101 study).

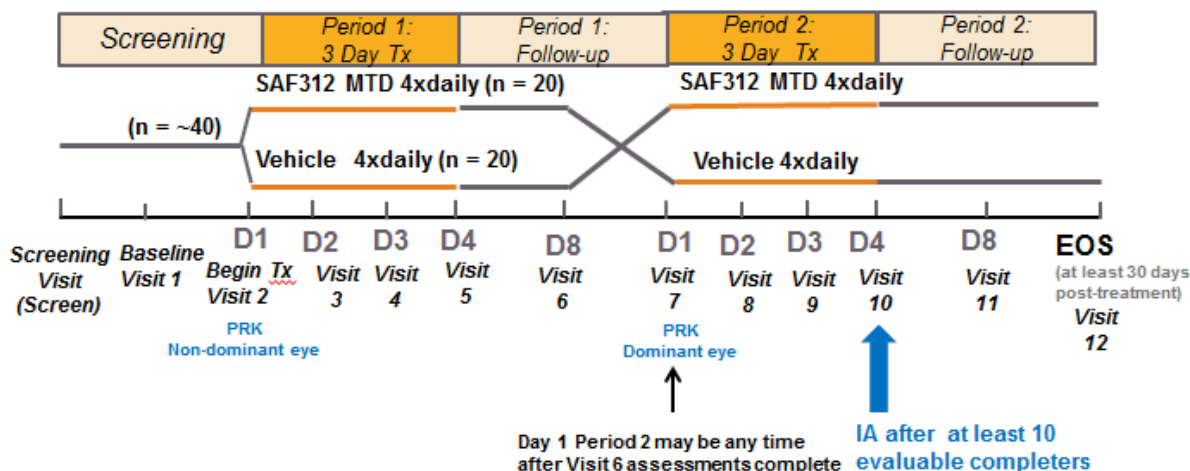
Approximately 40 patients will be randomized to two sequences to achieve about 30 evaluable patients: 1) SAF312, followed by placebo (n=20, or 2) placebo, followed by SAF312 (n=20. Each patient will receive the assigned dose, one drop four times daily for 72 hours following PRK surgery on their study eye (Day 1, Periods 1 and 2). The initial study eye will be the non-dominant eye as established at screening and in agreement of the patient and the PI. Each patient will return for follow-up visits on Days 2, 3, 4 and 8 of Period 1 after surgery in the first eye, with optional daily visits to follow the patient until wound healing is complete. If there is any complication or any reason to not have surgery in the second eye, the patient will not have the second eye surgery performed.

Patients will have PRK surgery on their second study eye (dominant eye) on Period 2, Day 1. The PRK surgery of the second eye should be performed after the epithelial defect of the first eye is resolved and at the discretion of the PI. After the second PRK, patients will receive the opposing treatment four times daily for 72 hours following the PRK surgery. Patients will return daily for the first 3 postoperative days (Period 2, Days 2-4) and at 1 week after the second surgery (Period 2, Day 8), with optional daily visits to follow the patient until wound healing is complete. An end of study (EOS) visit will take place 30 days after the second eye surgery (or after final dose of investigational product if the patient ends treatment early in period 1). To allow flexibility for scheduling the day of the second surgery, the day of the second PRK procedure (start of Period 2) may be as soon as Day 8 assessments are complete, or as long as six weeks after the first surgery.

All patients will receive standard of care treatment following PRK surgery, including application of a bandage contact lens (Air Optix® Night and Day® Aqua or equivalent) following the procedure and before receiving study drops for pain. A course of topical ocular antibiotic (Moxifloxacin or equivalent 1 eye drop four times daily) will be started after application of first dose of study drops and will be continued for 4-7 days. Prednisolone acetate ophthalmic 1 eye drop four times daily will be given for 1 week after PRK, followed by taper. Preservative-free unit-dose artificial tears may be used as needed. The first dose of study drops after each PRK procedure will be administered by site staff. Subsequent doses will be self-administered. Whenever drops are administered in sequence, at least 5 minutes must pass between eye drop administrations. To summarize, patients will undergo PRK procedure, bandage lens is placed on the cornea, SAF312 or placebo is given, after approximately 5 minutes antibiotic is given, and after another 5 minutes, prednisolone is administered. Detailed administration and assessment timing will be included in a table in the SOM.

Rescue medication will consist of oral analgesic (acetaminophen 300 mg + codeine 30 mg) as needed up to a total of 10 tabs/day or 1-2 tabs every 4 hours.

Figure 3-1 Study schedule



After at least 10 patients have had PRK surgery and study treatment for 72 hours in both eyes (completing Period 2, Day 4 visit), enrollment may be paused for an interim analysis (IA). Please see [Section 11.9](#) for details.

3.2 Rationale of study design

The rationale for the key elements of the study design are as follows:

- Bilateral cross-over design with interim analysis:** Cross-over design may be helpful in decreasing inter-patient variability because of different pain tolerance in different individuals. Capturing data from both eyes, in conjunction with an interim analysis after at least 10 evaluable patients (20 eyes) allows for an adjustment in the number of patients required to enable the decision to complete the study. There are no prior PRK pain studies with bilateral design, only with unilateral surgery, since unilateral PRK was the standard of care several decades ago when these studies were performed (in contrast to today's standard of bilateral simultaneous PRK). So, the interim analysis will estimate the inter-subject and intra-subject variability to confirm the power calculations for the whole study, and the sample size may be adjusted accordingly.
- Primary Endpoint (Electronic Patient Reported Outcome (ePRO) Visual Analog Scale (VAS) pain scale):** A validated electronic tool was selected to enable collection of sequential data. Previous studies of pain in PRK have shown that the most intense pain is experienced within the first 12 hours after surgery with the peak around 4-6 hours after surgery ([Sher et al 1993](#)), and these are the timepoints selected for primary endpoint analysis. Since we cannot be sure exactly when pain will be experienced by our patients in this study, and also it is important clinically to both try to decrease the maximum pain as well as the overall pain that the patient experiences during the immediate postoperative period, we decided to evaluate both 6 hours and the period up to 12 hours postoperatively, as primary endpoints.

- **Rescue oral analgesics:** It is not ethical to refuse pain control medication to patients postoperatively as part of a clinical trial, and all prior clinical trials of NSAIDs in postoperative pain after PRK used rescue oral analgesics, similar to the Standard of care after PRK. This can be a potential confounder of the pain VAS evaluation. We plan to use three approaches when analyzing pain VAS scores to account for the influence of pain meds (assuming 4 hours of rescue medication effect): (1) any recorded VAS score within 4 hours after use of rescue medication will be considered missing; (2) all the recorded VAS scores will be used; and (3) any recorded VAS scores within 4 hours after rescue medication use will be imputed by the record taken prior to the rescue medication. We will use the first approach as the primary analysis, and the other two for help with decision making.
- **Randomization and Masking** (Patient and investigator masked): Minimizes bias of investigators or subjects in assessing subjective readouts, such as adverse events or perception of pain (primary endpoint).
- **Patient population:** PRK is a common procedure with approximately 37,000 surgeries performed in the US in 2014 (<http://www.statista.com/statistics/271478/number-of-lasik-surgeries-in-the-us/>). The patient population is relatively homogeneous (usually under 45 years of age), with healthy corneas and eyes. The procedure results in a controlled, large, epithelial defect of 8mm with a consistent healing time of 3 to 4 days. Resultant pain is moderate to severe (especially the first day), often requiring oral narcotics or other pain killers. Pain after PRK is currently partially treated with Non-Steroid-Anti-Inflammatory (NSAID) or diluted anesthetic ocular drops; both groups of drugs have a side effect of delaying wound healing. There is no animal model for ocular pain control; however SAF312 when tested in an animal model of PRK in rabbits did not delay wound healing. Further, TRPV1 antagonists in mice and TRPV1 knock out mice showed no delayed corneal epithelial healing after injury ([Okada et al 2011](#); [Bates et al 2010](#)). There is an unmet medical need for pain control using a topical ocular drug that does not delay wound healing.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

SAF312 is a potent inhibitor of the transient receptor potential cation channel subfamily V member 1 (TRPV1). Oral SAF312 was effective in dental pain, but the development of oral SAF312 did not progress because of dose-dependent inhibition of noxious heat pain perception. SAF312 was developed as a topical ocular formulation for the treatment of ocular pain from corneal epithelial defect such as after PRK surgery. After PRK surgery the pain is the most intense during the first day after surgery and after the 3rd day (72 hours) it is much less, and at a level where topical ocular NSAIDs have no beneficial effect compared to placebo ([Sher et al 1993](#)). So, the duration of treatment with SAF312 after PRK surgery in the PoC study, is planned for 3 days (72 hours) after surgery.

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In this PoC study we plan to use the topical ocular dose of a single eye drop of
suspension, administered four times daily to a single
eye
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The proposed total daily dose of 3.7 mg of SAF312 from topical ocular 4-times daily
administration of a single eye drop of suspension dose is 13.5 -fold
lower than the total daily oral dose of 50 mg (from 25 mg twice daily dose regimen) which is
the lowest dose at which impaired heat perception was reported in humans.
Preliminary assessment of exposure data in humans indicates relative bioavailability of
Corporate Confidential Information suspension topical ocular dose compared to 25 mg oral dose,
therefore, lower systemic exposures are anticipated from the proposed ocular dose than the
oral dose.
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3.4 Rationale for choice of comparator

Vehicle eye drops will be used as a placebo to mask and compare efficacy and enable better determination of the relation of any observed ocular adverse events to SAF312.

3.5 Rationale for choice of background therapy

Current standard of care treatment after PRK include bandage contact lens, antibiotic, steroid anti-inflammatory, preservative-free artificial tears as well as oral and topical pain control medication, as per each surgeons preferences ([Woreta et al 2013](#)). In the current study, we keep all the parts of the standard of care treatment after PRK, with the exception of replacing topical ocular pain control medication with either SAF312 or placebo, but keeping oral pain control rescue medication in place to allow pain control and relief for the patient.

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3.7 Risks and benefits

There is no benefit expected for subjects participating in this study. If SAF312 is shown in the future to provide superior analgesic effect compared to current standard of care (NSAIDs or diluted topical anesthetic), the patient may experience better analgesia postoperatively during the period treated with SAF312 (but not during the vehicle-treated period), but at present there is no information available on analgesic effect of SAF312.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, continuous monitoring of masked emerging safety and tolerability data and stopping rules.

Potential risks associated with SAF312 (please note different risk profile for topical ocular versus oral systemic administration)

Topical Ocular SAF312

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- **Ocular safety and tolerability was excellent without dose limiting adverse events.**
All dose cohorts in the single and multiple ascending parts of the study, showed no dose limiting adverse events and the maximum feasible concentration is accepted in the maximum tolerated dose
All adverse events of suspected causality to SAF312 were

of mild severity, except for moderate severity eye irritation that lead to discontinuation of treatment in one patient of the cohort. The most frequent ocular adverse events in the SAF312 treated patients were corneal staining, hyperemia and mild anterior chamber inflammation, in levels similar to placebo (more details in the Investigators Brochure).

- **Systemic safety and tolerability of ocular SAF312 was excellent without dose limiting adverse events, including no evidence of risks identified with oral SAF312.**

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Oral systemic SAF312 compound specific risks based on clinical safety and tolerability are:

- **Impaired temperature perception/sensation neurologic risk.** The most commonly reported AEs in subjects dosed with SAF312 were transient sensation of cold and chills. At the highest tested single doses (800 and 1050 mg) some prolonged sensory neurologic changes with intact sensory and motor nerve conduction were observed. However, this risk is negligible as the dose used in this study is much lower. Dose-dependent changes in thermal perception (noxious heat) were noted as assessed by the “hand immersion test” (water at 49°C) as part of the multiple dose study and in the dental pain study. Altered thermal perception was dose-dependent and a dose of 12.5 mg or 15 mg lacked relevant effects on heat pain perception. Based on the data it is concluded that doses of 15 mg SAF312 or less allow for outpatient studies. In order to prevent potential injuries resulting from altered thermal perception a series of precautionary measures are implemented in all future clinical studies of oral SAF312.
- **Autonomic dysreflexia in patients with spinal cord injury.** One of the two patients treated with oral SAF312 for neurogenic detrusor overactivity due to spinal cord lesions developed circulatory collapse, headache, nausea, vomiting, and temperature regulation disorder as part of autonomic dysreflexia. Patients with an impaired autonomous nerve system (e.g. as consequence of spinal cord injury) may have a higher risk for developing autonomic dysreflexia and should not be treated with SAF312 or other TRPV1 receptor inhibitors.

- **Hyperthermia.** Transient increases in body temperature were observed in subjects dosed with SAF312 and these were generally not associated with clinically relevant changes in blood pressure or pulse. At repeat doses of 25 mg a mild transient elevation in body temperature was observed and at 12.5 mg SAF312 all reported body temperatures were within the normal range.
- **QT interval shortening.** The clinical studies performed with SAF312 demonstrated transient shortening of the QT interval; none of the QT interval changes was symptomatic or associated with clinically relevant arrhythmias (ventricular or supraventricular). The lowest QTcF value noted during the single oral dose study was 342 milliseconds (ms) and was observed on day 1 at 1-2 hours post-dosing in one subject in each of the three different dosing groups (i.e., 7.5, 125 and 1050 mg). The lowest QTcF values observed in the multiple dosing study were between 355 ms and 364 ms, except one subject (Part B) who was discontinued from the study due to a shortened QTcF of 333 ms compared to 351 ms at baseline, with no associated arrhythmia after a single dose of 125 mg SAF312. The minimum QTcF value measured in patients with post-operative pain treated with SAF312 was 347 ms (one subject). The clinical relevance of drug - induced short QTcF intervals of this magnitude is presently unknown. Recently, ([Anttonen et al 2007](#)) reported that a short QTcF interval (<340 ms) was not associated with a higher mortality in a population of non-referral middle-aged subjects.

Women of child bearing potential should be informed that taking the investigational drug may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

There may be unknown risks of SAF312 which may be serious.

3.7.1 Blood sample volumes

A maximum of approximately 72 mL of blood is planned to be collected from each subject as part of the study. Additional samples for serum pregnancy test and monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment schedule, [Section 8.1](#).

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage, and shipment information.

See [Section 8.9](#) regarding the potential use of residual samples.

4 Population

Male and female patients who are eligible for PRK surgery and between 18 and 75 years old (inclusive). The study plans to enroll approximately 40 patients to achieve about 30 evaluable completers. Sample size may be adjusted based on the interim analysis.

Subject selection is to be established by checking through all eligibility criteria at screening, with confirmation of select eligibility criteria at baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site. Deviation from **any** entry criterion excludes a subject from enrollment into the study. Additional subjects may be enrolled when subjects discontinue the study for reasons other than safety. All patients exposed to investigational product will be included in some analyses such as patients who discontinued or who only had surgery in one eye will be included in safety analysis (details in the analysis plan).

4.1 Inclusion criteria

Population eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Male and female patients age 18 to 75 who are eligible for bilateral PRK surgery.
2. Normal eye exam except for refractive error at baseline.
3. Planned myopia correction should not exceed -4.00 Diopters (sphere) and 3.00 diopters of astigmatism, with spherical equivalent not higher than -4.50, confirmed by manifest refraction at baseline. Monovision treatment is allowed.
4. Written informed consent must be obtained before any assessment is performed.

4.2 Exclusion criteria

Population fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Monocular patient (including amblyopia) or best corrected visual acuity score worse than 20/80 (Snellen) or 55 letters (EDTRS), at baseline.
2. Any systemic or ocular disease that might affect wound healing (such as severe rheumatoid arthritis or diabetes or history of keloid formation) or a history of ocular trauma, uveitis, infection, or inflammation in the 6 months prior to baseline.
Especially for diabetes: Patients with severe diabetes, uncontrolled diabetes, diabetic keratopathy, diabetic retinopathy, diabetic macular edema, diabetic nephropathy, diabetic foot ulcers or other systemic complications of diabetes are excluded. Patients with mild, well controlled diabetes with no evidence of ocular or systemic complications of diabetes can be included.
3. Patients with active inflammatory or infectious ocular conditions, severe or progressive retinal disease, and use of topical or systemic steroids, or use of coumadin or similar drugs within the last 6 months prior to baseline.
4. Patients with any corneal dystrophy (epithelial, stromal or endothelial) or any cornea disease (including significant scarring (at the discretion of the PI), ocular herpes or pterygium).
5. Previous refractive or corneal surgery (such as LASIK, PRK, radial keratotomy, pterygium removal, corneal transplantation).

6. History of allergic or hypersensitivity reaction or significant adverse events to any of the drugs to be used in this study including:
 - tetracaine or similar topical ocular anesthetic
 - NSAIDs and aspirin
 - oral analgesic (including acetaminophen and codeine)
 - antibiotics
 - steroids
 - inability to tolerate or wear bandage contact lens

7. Chronic pain of any etiology or any significant illness which has not resolved within two (2) weeks prior to initial dosing.

8. Concurrent therapy or history of chronic therapy or abuse of systemic or ocular NSAIDs, analgesics, pain medication (including gabapentin or pregabalin and similar), opiates or cannabis.

Patients with use of any topical eye medication except for lubricating eye drops within two weeks prior to surgery, in the study eye will be excluded.

Patients meeting any of the following will also be excluded:

- (a) any use of topical NSAIDs during 30 days before baseline, OR
 - (b) systematic/chronic use of systemic NSAIDs within 30 days prior to baseline, OR
 - (c) occasional use of systemic NSAIDs within 3 days prior to baseline, OR
 - (d) use of ocular cyclosporine (or similar medication) within the 3 months prior to surgery.
9. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days of baseline, whichever is longer; or longer if required by local regulations.
 10. History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing. Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
 11. Subjects using CPAP or other sleep apnea devices.
 12. Subjects who do not weigh at least 50 kg, or who do not have a body mass index (BMI) within the range of 18 - 35 kg/m². BMI = Body weight (kg) / [Height (m)]²
 13. Pregnant or nursing (lactating) women.
 14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. **Basic contraception methods include:**
 - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should be stable on the same pill for a minimum of 3 months before taking study drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

15. Unable to communicate well with the investigator, to understand and comply with the requirements of the study including use of ePRO device at home and adherence to the dosing and visit schedule.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

A corneal and eye examination consistent with eligibility for PRK surgery is needed at baseline.

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Please refer to exclusion criteria ([Section 4.2](#)) for details of contraception requirements for the study.

5.2 Prohibited treatment

No ocular medication other than study drugs (study drugs include standard of care drugs such as antibiotic and steroid, as well as preservative free artificial tears) will be allowed from the first dosing until all of the Study Completion evaluations have been conducted. All drugs, including artificial tears are stored and administered at room temperature only (refrigerated/cold eye drops are not allowed with the exception of use during PRK surgery inside the operating room if desired by surgeon).

Mitomycin C must not be used as an intraoperative medication for patients on this study.

No pain medication may be used within 24 hours prior to surgery. No pain medication other than rescue analgesics may be used from surgery until 4 days post-surgery for ocular or periocular pain. If a patient requires analgesics at the time scheduled for the second surgery, the PI and patient must decide whether the patient will discontinue use of pain medication 24 hours prior to the scheduled surgery (if medically feasible) or postpone the surgery until analgesic use is discontinued.

Should a subject have an *incidental and limited* need for a medication to be taken at any point during the study (e.g. antibiotic prophylaxis prior to dental surgery or for pain relief of pain in any other part of the body or fever, limited use of acetaminophen [e.g., up to 2 tablets of 325mg, or ibuprofen up to 2 tablets of 200mg etc.]), the sponsor should be advised, as administration of any concomitant medication *may* require the subject to be withdrawn. Total acetaminophen dose must be less than 3g/day, including rescue analgesics and any incidental need for medication unrelated to ocular pain.

5.3 Dietary restrictions and smoking

- No cannabis use for 4 weeks before screening until after Study Completion evaluation.
- No cigarettes/use of nicotine products and no alcohol use for 24 hours before dosing and until after completion of study treatment (Day 4 in each period).

5.4 Other restrictions

- No strenuous physical exercise, particularly contact sports or other activities with a risk of contact to the eyes (e.g. basketball) until the later of: complete healing of epithelial defect following each surgery, OR at least one week after each surgery.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drugs

Table 6-1 Overview of study medication

Drug	Formulation	Appearance	Unit dose	Packaging	Provided by
SAF312	Topical ocular drops	Colorless to off-white clear liquid OR white to off-white uniform suspension	SAF312 per 37 µL drop size	Single use droppers (preservative free)	Alcon
SAF312 vehicle/Placebo	Topical ocular drops	Colorless to off-white clear liquid OR white to off-white uniform suspension	NA	Single use droppers (preservative free)	Alcon

6.1.2 Additional study treatment

Ancillary treatments will be provided by participating sites with funding provided by Sponsor. All patients will receive standard of care ancillary treatment following PRK surgery, including:

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- A course of topical ocular antibiotic (Moxifloxacin or equivalent 1 eye drop four times daily): start right after PRK surgery, and after application of first dose of study eye drop and continued for 4-7 days, per managing physician.
- Prednisolone acetate ophthalmic: 1 eye drop four times daily will be started right after PRK surgery and after instillation of antibiotic eye drop and will be given for 1 week after PRK, followed by taper per local procedures.
- Preservative-free unit-dose artificial tears may be used as needed. Artificial tears may **not** be chilled for analgesic effect.

Whenever drops are administered in sequence, at least 5 minutes must pass between eye drop administrations.

To summarize, patients will undergo PRK procedure, bandage lens is placed on the cornea, SAF312 or placebo is given, after approximately 5 minutes antibiotic is administered, and after another 5 minutes, prednisolone is administered. Detailed administration and assessment timing are included in Table 1-1 of the SOM.

Ancillary medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.2 Treatment arms

Subjects will be assigned to one of the following 2 treatment sequences in a ratio of 1:1 lasting 3 days per period.

Table 6-2 Definition of treatment sequences

Sequence	Period 1	Period 2
1	SAF312 4 times daily (every 6 hours) for 72 hours (inclusive)	Vehicle control to SAF312 4 times daily (every 6 hours) for 72 hours (inclusive)
2	Vehicle control to SAF312 4 times daily (every 6 hours) for 72 hours (inclusive)	SAF312 4 times daily (every 6 hours) for 72 hours (inclusive)

6.3 Treatment assignment and randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of the Sponsor Biostatistics & Clinical Data Operations (Statistical Programming) Groups using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-masked study. Subjects and investigators will remain masked to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, and schedule of administration, and similar in appearance.

Site staff

With the exception of any unmasked site staff identified below, all site staff (including study investigator and study nurse) will be masked to study treatment throughout the study.

Unmasking a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see [Section 6.7](#)).

Sponsor staff

The following unmasked sponsor roles are required for this study:

- Unmasked sample analyst(s) (PK)

The sample analysts will receive a copy of the randomization schedule, to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under masked conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unmasked information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in [Table 6-3](#). For example, unmasked summaries and unmasked individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unmasked results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unmasked personnel will otherwise keep randomization lists and data or information that could unmask other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unmasked.

Table 6-3 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	B	B
Site staff	B	B	UI	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

SAF312 will be administered to the subject via the following route of administration: ocular drops. Drops will be administered at the study site by the study personnel during the day of surgery. During the daily follow up postoperative visits, if the patient is at the site during the expected time for eye drop administration, the study personnel may administer the eye drops. The remainder of drops will be home administered by the patient. See the Site Operations Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-masking can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in all subjects treated with SAF312, as detailed in [Section 8.7](#).

The investigator must promote compliance by instructing the subject to take the study treatment and rescue medication exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. Subjects will be instructed that failing to comply with study procedures, such as repeatedly missing doses of study medication or repeatedly entering incorrect rescue medication use information in the electronic Patient Reported Outcomes (ePRO) device may be removed from the study at the discretion of the investigator in coordination with the Sponsor. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit using rescue medication counts and ePRO information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Compliance must be reconciled against patient-reported use in the electronic diary at each applicable visit.

6.9 Recommended treatment of adverse events

AEs will be treated at the discretion of the Investigator and in accordance with current medical practice.

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The most common drug suspected adverse events in this study were: corneal staining, hyperemia and mild anterior chamber inflammation (more details in the IB).

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Ocular AEs should be treated according to the type of the AE.

Subjects should remain in the study even after receiving treatments for AEs until the Investigator feels that subject discharge is warranted.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

6.10 Rescue medication

Rescue medication is provided by the Sponsor, and will consist of oral analgesic (acetaminophen 300 mg + codeine 30 mg). Patients will be instructed to take as needed for pain relief up to a total of 10 tabs/day or 1-2 tabs every 4 hours during the treatment period (Visits 2-5 and 7-10). Patients must be instructed to complete a VAS for pain assessment prior to taking rescue medication.

Use of pain medication after the treatment period (after visits 5 and 10) is per PI discretion, and must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.11 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Both temporary and permanent punctal plugs are allowed at the discretion of the PI, but must be recorded on the Concomitant Medication or Medical History form, respectively.

Benzodiazepines and similar medication are allowed in moderation and if absolutely necessary for a specific patient on a case by case basis, on day of surgery only.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

The final study visit is conducted at least 30 days after final treatment (study medication) and will serve as safety follow-up. Any subjects who discontinue the study after receiving treatment or are otherwise not seen at the final visit should, at a minimum, have a safety follow-up call conducted at least 30 days after the last study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 9.2](#) and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Any adverse event graded severe or higher (see severity grading in [Section 9.1](#)) related to study drug
- Emergence of the following adverse events:
 - Severe or persistent moderate ocular discomfort as reported by the subject that is outside the expected discomfort from PRK surgery
 - Cornea or ocular surface epithelial defects (extensive and non-healing) that are outside the expected extent and rate of healing after PRK surgery
 - Any condition requiring additional or new intraocular surgery (concurrent or after the PRK surgery) in the study eye
 - Any severe intraoperative complication occurred during the PRK surgery. In this case the patient will be withdrawn from the study and will not be dosed with any dose of the investigational drug.
- Any protocol deviation that results in a significant risk to the subject's safety

Discontinuation of Study/investigational treatment will be at the discretion of the Investigator, under the following circumstances:

- Emergence of the following adverse events:
 - Any need for eye surgery (outside the planned bilateral PRK)
 - A serious adverse event that, in the opinion of the investigator, is not related to the study drug
 - Temperature increase to $> 39.0^{\circ}\text{C}$ measured orally which is sustained for >15 minutes at any time
 - Hyperthermia ($> 38.0^{\circ}\text{C}$)-related changes in vital signs which are judged as clinically significant by the investigator (an increase in heart rate to > 120 BPM and/or a drop in blood pressure to $<80/40$ mmHg)
 - \geq Grade 2 hypertension (≥ 24 hour or symptomatic increase in BP by > 20 mmHg (diastolic) or to $> 160/100$)
 - \geq Grade 2 intraocular inflammation
 - Corneal edema/corneal opacity \geq Grade 1

The appropriate personnel from the site and the sponsor will assess whether study and investigational treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see protocol [Section 7.3](#)). Where possible, they should return for the assessments indicated at EOS visit in the [Assessment schedule](#). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and/or letter) should be made to contact them as specified in protocol [Section 7.4](#).

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

Under any of the following conditions, the current study/part will be placed on temporary hold and potentially halted, pending full review of the clinical data by the investigator and Sponsor:

- Two or more incidents of a similar serious adverse event that, in the opinion of the investigator, are related to the study drug
- The principal investigator and the sponsor consider that the number and/or severity of adverse events justify discontinuation of the study.
- Any severe or higher adverse event (see severity grading in [Section 9.1](#)) related to study drug
- The Sponsor requests it.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Study Phase	Screening	Baseline	Treatment 1 ²								Treatment 2 ²								End of Study or Early Exit
Visit Numbers ¹	Screen	1	2	3	4	5	Opt*	6 ²	Opt*	7 ²	8	9	10	Opt*	11	Opt*	12		
Study Day(s)	-29 to -2	-1 -14 +0	1	2	3	4	5-7	8	9 or later	1	2	3	4	5-7	8	9 or later	30 days post-last dose (study med)		
Time (post-initial dose of treatment cycle)	-	-	0h	1h	24h	48h	72h	74h	-	-	0h	1h	24h	48h	72h	74h	-	-	
Informed consent	X																		
Corporate Confidential Information																			
Inclusion / Exclusion criteria	X	X																	
Medical history/current medical conditions	X	X																	
Ocular history	X	X																	
Demography	X																		
Pregnancy test ³	X	X															X		
Drug screen	X				X							X							
Blood Pressure and Pulse Rate	X	X	X ⁴		X ⁴	X ⁴	X ⁴		X		X ^{4,2}		X ⁴	X ⁴	X ⁴		X	X	

Study Phase	Screening	Baseline	Treatment 1 ²									Treatment 2 ²									End of Study or Early Exit
Visit Numbers ¹	Screen	1	2	3	4	5	Opt*	6 ²	Opt*	7 ²	8	9	10	Opt*	11	Opt*	12				
Study Day(s)	-29 to -2	-1 -14 +0	1	2	3	4	5-7	8	9 or later	1	2	3	4	5-7	8	9 or later	30 days post-last dose (study med)				
Time (post-initial dose of treatment cycle)	-	-	0h	1h	24h	48h	72h	74h	-	-	0h	1h	24h	48h	72h	74h	-				
Body temperature	X	X	X ⁴		X ⁴	X ⁴	X ⁴			X		X ^{4,2}	X ⁴	X ⁴	X ⁴		X				
Body weight	X																X				
Body height	X																				
Concomitant therapies		As required															X				
Adverse events		As required															X				
Serious adverse events		As required																			
Corporate Confidential Information			X ⁵																		
PK blood collection ⁶			See table below																		
PRK Procedure ⁷			SE								SE ⁴										
Corporate Confidential Information		X			X ⁴		X ⁴		X				X ⁴		X ⁴		X				
VAS (Visual Analog Scale) pain assessment ⁸		X	X								X										
Patient diary ⁸			X								X										

Study Phase	Screening	Baseline	Treatment 1 ²									Treatment 2 ²									End of Study or Early Exit
Visit Numbers ¹	Screen	1	2	3	4	5	Opt*	6 ²	Opt*	7 ²	8	9	10	Opt*	11	Opt*	12				
Study Day(s)	-29 to -2	-1 -14 +0	1	2	3	4	5-7	8	9 or later	1	2	3	4	5-7	8	9 or later	30 days post-last dose (study med)				
Time (post-initial dose of treatment cycle)	-	-	0h	1h	24h	48h	72h	74h	-	-		0h	1h	24h	48h	72h	74h	-			-
Oral analgesics use ⁹					X	X	X							X	X	X					
Blink Rate	OU ¹⁰	OU	OU ⁴		OU ⁴	OU ⁴	OU ⁴			OU		OU ^{4,2}		OU ⁴	OU ⁴	OU ⁴			OU		OU
Corporate Confidential Information	See table below																				
Visual acuity	OU ¹⁰	OU			SE ⁴	SE ⁴	SE ⁴			OU				SE ⁴	SE ⁴	SE ⁴			SE		OU
Dominant eye test	X ^{7,12,10}																				
Ocular hyperemia	OU ¹⁰	OU	SE ⁴		SE ⁴	SE ⁴	SE ⁴			OU		SE ^{4,2}		SE ⁴	SE ⁴	SE ⁴			SE		OU
Slit lamp biomicroscopy	OU ¹⁰	OU	SE ⁴	SE	SE ⁴	SE ⁴	SE ⁴			OU		SE ^{4,2}	SE	SE ⁴	SE ⁴	SE ⁴			SE		OU
Corneal Staining	OU ¹⁰	OU								OU ¹³									OU ¹³		OU
Corporate Confidential Information				SE	SE ⁴	SE ⁴	SE ⁴		SE*	SE*	SE*		SE	SE ⁴	SE ⁴	SE ⁴		SE*	SE*	SE*	
		OU		SE ¹⁴		SE ⁴	SE ⁴		SE*	SE*	SE*		SE		SE ⁴	SE ⁴		SE*	SE*	SE*	
Tear Production	OU ¹⁰	SE						SE		OU							SE		SE		OU

[illegible]

¹ Visit structure given for internal programming purpose only

² Treatment Period 2 may begin any time after wound closure from Period 1 surgery and Day 8 assessments completed (including on Day 8), and up to 6 weeks post first surgery. If Day 1 of Treatment Period 2 is less than 1 week from Day 8 of Treatment Period 1, pre-dose ocular and vital sign assessments (e.g., Blink rate, Body temperature) do not need to be repeated.

³ Serum test at baseline with urine pregnancy test by local standards for other timepoints

⁴ Pre-dose (prior to PRK, as applicable)

⁵ PG sample may be drawn at any timepoint if missed at designated timepoint

⁶ Patient may decline any PK blood draw and remain in the study with the agreement of the PI and sponsor

⁷ First and second study eye (SE) will be established based on results of the dominant eye test. SE will preferably be the non-dominant eye in the first treatment period, subject to investigator treatment decision.

⁸ ePRO VAS pain scores, study and rescue medication dose diary, and related questions will be collected at pre-specified time points (pre-dose, 1 hour, 3 hours, 6 hours, 9 hours, 12 hours and prior to every dose until day 5 post-operatively) as instructed by the ePRO and described in the SOM. VAS pain scores will also be collected for up to 24 hours following the final dose in each period, as detailed in the ePRO. In addition, for both periods 1 and 2, the following timepoints will include VAS pain scores at pre-dose (as stated above) AND 30 minutes after dose: hours 6 (+30 minutes), 18 (+30 minutes), 24 (+30 minutes), and 30 (+30 minutes). ePRO devices will be collected when all assessments are complete.

⁹ As collected by the site staff at each post-surgery visit (Days 1-4 in each period)

¹⁰ Corporate Confidential Information e used as screening values rather than repeating assessments.

Study eye for current period = SE, assessments on both eyes = OU

¹³ If bandage contact lens is still in place at Visit 6 or 11 (Study Day 8 for either period), corneal staining will not be performed.

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ge contact

lens needs to be replaced prior to day 4, attempt to retrieve and store all used lenses.

¹⁶ Optional per Sponsor

* Patients may be followed for wound closure, at PI discretion, on study Days 5-7 or after Day 8, until wound is completely healed. On those visits, wound size estimation by slit lamp should be performed, preferably by the same examiner, along with anterior segment OCT, if available, at Sponsor's option. Other assessments are at PI discretion. These additional visits and assessments will be optional for both sites and patients.

Table 8-1 Details for highly repetitive assessments

Study Phase	Visit	Day	Time (post-dose)	PK blood collection
Screening	Screen	-29 to -2	-	
Baseline	1	-1 -14 +0	-	
Treatment 1 ³	2	1	Prior to dose	Prior to dose ⁴
			0.25h	X
			0.5h	X
			1h	X
			2h	X
	3	2	24h	Prior to dose
	4	3	48h	
	5	4	72h	Prior to dose
			72.25h	X
			72.5h	X
			73h	X
			74h	X
	6 ³	8	-	
Treatment 2 ³	7 ³	1	Prior to dose	Prior to dose ⁴
			0.25h	X
			0.5h	X
			1h	X
			2h	X
	8	2	24h	Prior to dose
	9	3	48h	
	10	4	72h	Prior to dose
			72.25h	X
			72.5h	X
			73h	X
			74h	X
	11	8	-	
End of Study or Early Exit	12	30 days post-last dose (study med)	-	

¹ Patient may decline any PK blood draw and remain in the study with the agreement of the PI and sponsor

² Participating sites only, testing is at the Sponsor's option

³ Treatment Period 2 may begin any time after Day 8 assessments completed (including on Day 8), and up to 6 weeks post first surgery. If Day 1 of Treatment Period 2 is less than 1 week from Day 8 of Treatment Period 1, pre-dose ocular and vital sign assessments (e.g., Blink rate, Body temperature) do not need to be repeated.

⁴ Prior to PRK

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

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A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.3 Subject screening

Re-screening will be allowed in communication with the Sponsor, on a case-by-case basis. Re-screened subjects will keep their original screening numbers.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Drug screen

Drug test for drugs of abuse will be conducted at screening. Testing to assess use of rescue medication will be conducted during treatment. Samples will be sent to a central lab. Results will be kept as source documentation. Central lab details are included in central laboratory manual.

8.5 Efficacy / Pharmacodynamics

8.5.1 VAS (Visual Analog Scale) pain assessment

VAS pain scores, study and rescue medication dose diary, and related questions will be entered in a provided device. See SOM for details.

8.5.2 Oral analgesics use

Rescue medication use will be recorded in the eCRF and reconciled with patient entries in the provided electronic device. See SOM for details.

8.5.3 Patient diary

VAS pain scores, study and rescue medication dose diary, and related questions will be entered in a provided device. See SOM for details.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule ([Section 8.1](#)) detailing when each assessment is to be performed.

8.6.1 Body temperature

See SOM for details.

8.6.2 Blood Pressure and Pulse Rate

See SOM for details.

The CRF should contain the blood pressure and pulse rate measurements.

8.6.3 Blink Rate

Blink rate will be assessed as blinks per 1 minute, as per SOM and [Assessment schedule](#). This data will be included in the clinical study report.

8.6.4 Visual acuity

Best-corrected visual acuity and uncorrected visual acuity, together with the refractive correction (if checked) will be obtained in each eye separately. This assessment is to be performed prior to pupil dilation. The results will be recorded in the appropriate eCRF page.

8.6.5 Slit lamp biomicroscopy

Slit lamp exam of the adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens and undilated fundus exam will be obtained for each subject according to the [Assessment schedule](#). Results from the slit lamp biomicroscopy exam will be recorded in the appropriate eCRF page.

8.6.6 Intraocular Pressure (IOP)

See SOM for details.

8.6.7 Dilated fundus exam

Dilated fundus exam will be obtained for each subject according to the [Assessment schedule](#).

8.6.8 Ocular hyperemia

Ocular hyperemia will be assessed by simple live scoring at the timepoints shown in the [Assessment schedule](#). For more details refer to the SOM. This data will be included in the clinical study report.

8.7 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment schedule, [Section 8.1](#). Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. See [Section 8.9](#) regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

SAF312 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLQ) in plasma is 0.05 ng/mL. Concentrations will be expressed as ng/mL. If feasible, bandage contact lenses (BCL) exposed to study drug may be analyzed for residual drug exposure after treatment. The bioanalysis of SAF312 in BCL will be exploratory, and the LC/MS/MS method used for the purpose may not be validated. Concentrations below the LLQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters may be determined as relevant using the actual recorded sampling times using non-compartmental method(s) with Phoenix™ WinNonlin® (Version 6.4 or higher): C_{max}, C_{min} (pre-dose), T_{max}, AUC_{last}, AUC_{0-t}, C_{last} and T_{last} from the plasma concentration-time data. Other PK parameters maybe calculated if deemed necessary. The linear trapezoidal rule will be used for AUC calculation.

8.8 Other assessments

8.8.1 Ocular assessments

8.8.1.1 Dominant eye test

The dominant eye and the non-dominant eye of each subject will be identified with the dominant eye test. In each study period, one eye (the subject of the PRK surgery) will be selected as the study eye (SE). SE will preferably be the non-dominant eye in the first treatment period, subject to investigator treatment decision.

8.8.1.2 Wound size estimation by slit lamp exam

Adjust slit beam and angle of illumination to allow visualization of the corneal wound boundary. Adjust beam height to approximate maximum horizontal (wound width) and vertical (wound height) of the surgical epithelial wound in millimeters.

8.8.1.3 Tear Production

Tear production will be evaluated by Shirmer's test, as per SOM and [Assessment schedule](#). This data will be included in the clinical study report.

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8.8.2 Corneal Staining

Corneal staining will be determined on a scale of 0-3 as the average from each of 5 zones (central plus 4 quadrants). Results will be recorded for each zone. This test will be performed using a slit lamp after instilling fluorescein into the lower palpebral conjunctiva of both eyes.

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See [Section 9.5](#) for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Instructions for reporting of adverse events commonly associated with PRK surgery have been added to the SOM.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
2. its relationship to the study treatment
 - Yes or
 - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see [Section 9.2](#) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
All adverse events must be treated appropriately. Treatment may include one or more of the following:
 - no action taken (e.g. further observation only)
 - investigational treatment dosage increased/reduced
 - investigational treatment interrupted/withdrawn
 - concomitant medication or non-drug therapy given
 - hospitalization/prolonged hospitalization (see [Section 9.2](#) for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study) and has not worsened since the start of study drug
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per [Section 9.2.2](#).

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last study treatment must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

9.3 Reporting Medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. [Table 9-1](#) summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see [Section 9.1](#) and [Section 9.2](#), respectively.

9.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

9.5 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Sponsor. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and [Assessment schedule](#) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

Novartis staff or CRO staff working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

Diary and PRO data will be entered into an electronic diary by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

10.4 Data Monitoring Committee

Not required

10.5 Adjudication Committee

Not required

11 Data analysis

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The primary PD analysis set will include all subjects who completed treatment through Day 4 in both eyes/treatment periods with available PD data, and with no protocol deviations that impact PD data. The secondary PD analysis set will include all subjects (completers and non-completers) with available PD data, and with no protocol deviations that impact PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

11.4 Analysis of the primary variable(s)

The primary aim of this study is to evaluate the efficacy of SAF312 eye drops on the pain in the immediate post-operative period.

11.4.1 Variable(s)

The primary variables are visual analog scale (VAS) pre-dose pain assessment at 6 hours post-operatively, and the average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment.

11.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy analysis will assess the effect of SAF312 eye drops on the visual analog scale (VAS) pain assessment prior to the 6 hour dose post-operatively compared to vehicle, and the average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment compared to vehicle.

A longitudinal mixed effect model accounting for the cross-over effect with repeated measurement for VAS will be used. The model will include fixed effects of treatment, hour post-operatively, period, sequence, the treatment-by-hour post-operatively interaction, the hour post-operatively-by-period interaction, and the hour post-operatively-by-sequence interaction. Repeated measurement over hour post-operatively-by-period for each subject will be accounted for using the unstructured covariance matrix. Kenward-Roger method will be used for approximating the denominator degrees of freedom. Least square means will be estimated for each treatment-by-hour post-operatively combination and the corresponding 90% confidence intervals will be obtained. The difference between SAF312 and vehicle, the p-value, and the corresponding 90% confidence interval will be obtained from the model at each time point.

A mixed effect model accounting for the cross-over effect for natural logarithmic transformed average (0-12hr) will be used. The model will include fixed effects of treatment, period, and sequence and a random effect of subject. Kenward-Roger method will be used for approximating the denominator degrees of freedom. Least square geometric means will be estimated for each treatment and the corresponding 90% confidence intervals will be obtained. The difference between SAF312 and vehicle, the p-value, and the corresponding 90% confidence interval will be obtained from the model.

Efficacy analyses will be performed on both of the primary PD dataset (completers only) and the secondary PD dataset (completers and non-completers). Completers are defined as patients who completed treatment through Day 4 in both eyes / treatment periods. The primary efficacy analysis will be the one based on the primary PD dataset.

11.4.3 Handling of missing values/censoring/discontinuations

An additional equal number of subjects may be enrolled for subjects who withdraw from the study for reasons other than safety. Decisions regarding enrollment of these additional subjects will be discussed with the sponsor on a case-by-case basis.

11.4.4 Sensitivity analyses

To account for the potential influence of the rescue medication on the primary endpoints, we plan to use three different approaches of analyzing the VAS pain scores and calculating the average (0-12hr) (assuming that the influence window of rescue medication is 4 hours): (1) any recorded VAS pain score at time points within 4 hours of the use of rescue medication will be considered missing; (2) all the recorded VAS pain scores will be used; (3) any recorded VAS pain score at time points within 4 hours of the use of rescue medication will be imputed by the record taken prior to the use of rescue medication. We will use the first approach as the primary analysis, and the other two for help with the decision making.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The secondary efficacy analysis will assess the effect of SAF312 eye drops on whether patients need oral analgesics in 12 hours, 24 hours, 2 days, and 3 days post-operatively compared to vehicle, as well as the amount of oral analgesics needed in 12 hours, 24 hours, 2 days, and 3 days post-operatively compared to vehicle. Number of patients who do not use oral analgesics from each treatment group will be reported by each assessment time post-operatively. McNemar's test will be used to analyze the difference of the numbers of patients who take or do not take oral analgesics between SAF312 and vehicle. The amount of oral analgesics needed will be analyzed at each assessment time post-operatively. Efficacy analyses will be performed on both of the primary PD completer-only dataset (completers only) and the secondary PD all-subject dataset (completers and non-completers). Completers are defined as patients who completed treatment through Day 4 in both eyes / treatment periods.

11.5.2 Safety

The following safety assessments will be descriptively analyzed:

- AEs and SAEs
- Vital signs (blood pressure, pulse rate, and body temperature)
- Ocular assessments
 - Visual acuity
 - Intraocular pressure (IOP)
 - Dilated fundus exam
 - Ocular hyperemia
 - Size of epithelial defect by slit lamp exam
 - Blink rate
 - Tear production
 - Epithelial defects

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time, and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period/epoch and continuing into the next period/epoch is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period/epoch is only counted once towards the total of this body system and treatment.

Ocular assessments

All ocular assessments will be listed by treatment, subject, visit/time and eye. Summary statistics will be provided descriptively by treatment, visit/time and eye.

11.5.3 Pharmacokinetics

SAF312 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point including the frequency (n) of concentrations.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. PK parameters will be calculated as described in [Section 8.5](#) and will be listed by treatment and subject.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

There are no known PD markers to be evaluated in the study. However, ocular surface temperature is being explored as a potential biomarker.

11.5.5 Other assessments

Not applicable

11.7 Sample size calculation

The study will be considered positive if:

- ocular pain VAS at 6 hours post-operatively for SAF312 is statistically significantly lower compared to vehicle, OR
- average of ocular pain VAS up to 12 hours post-surgery (average 0-12 hrs) for SAF312 is statistically significantly lower compared to vehicle.

This study will randomize approximately 40 patients in a 1:1 ratio between two sequences, to provide approximately 30 patients (60 eyes) evaluable for the primary endpoints. A total of 60 eyes will provide approximately 83% power to reject the null hypothesis of equality of mean VAS at the 0.1 level of significance (two-sided) in unilateral parallel design, assuming a treatment difference of 20 mm and standard deviation of 30 mm. The basis for the treatment difference assumption is [Sher et al 1993](#), which is a study comparing Diclofenac to vehicle on pain severity in PRK subjects wherein a treatment difference ranging from 15 mm to 30 mm

(adjusted for a 100 mm scale) was reported between 6-hour and 12-hour post PRK with maximum difference observed at about 6-hour post PRK time point. With bilateral cross-over design, the power is expected to be higher than that estimated from the unilateral parallel design as we expect high correlation between the two eyes from the same subject. While there is no adequate data to inform exact sample size calculation for the average (0-12 hrs) endpoint, we assume that the sample size based on the mean VAS will also be adequate for the comparison based on the average (0-12 hrs) endpoint.

11.8 Power for analysis of key secondary variables

Not applicable

Corporate Confidential Information

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 9](#) (Safety Monitoring) must be followed and the Study Lead informed.

14 References

- Anttonen O, Junttila MJ, Rissanen H, et al (2007) Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. *Circulation* p. 714-20.
- Bates BD, Mitchell K, Keller JM, et al (2010) Prolonged analgesic response of cornea to topical resiniferatoxin, a potent TRPV1 agonist. *Pain* p. 522-8.
- Mergler S, Valtink M, Coulson-Thomas VJ, et al (2010) TRPV channels mediate temperature-sensing in human corneal endothelial cells. *Exp. Eye Res.* p. 758-70.
- Murata Y, Masuko S (2006) Peripheral and central distribution of TRPV1, substance P and CGRP of rat corneal neurons. *Brain Res.* p. 87-94.
- Okada Y, Reinach PS, Shirai K, et al (2011) TRPV1 involvement in inflammatory tissue fibrosis in mice. *Am. J. Pathol.* p. 2654-64.
- Pan Z, Wang Z, Yang H, et al (2011) TRPV1 activation is required for hypertonicity-stimulated inflammatory cytokine release in human corneal epithelial cells. *Invest. Ophthalmol. Vis. Sci.* p. 485-93.
- Qazi Y, Hurwitz S, Khan S, et al (2016) Validity and Reliability of a Novel Ocular Pain Assessment Survey (OPAS) in Quantifying and Monitoring Corneal and Ocular Surface Pain. *Ophthalmology* p. 1458-68.
- Sher NA, Frantz JM, Talley A, et al (1993) Topical diclofenac in the treatment of ocular pain after excimer photorefractive keratectomy. *Refract Corneal Surg* p. 425-36.
- Sumioka T, Okada Y, Reinach PS, et al (2014) Impairment of corneal epithelial wound healing in a TRPV1-deficient mouse. *Invest. Ophthalmol. Vis. Sci.* p. 3295-302.
- Woreta FA, Gupta A, Hochstetler B, et al (2013) management of post-photorefractive keratectomy pain. *Survey Ophthalmology* 58(6):529-35.
- Yang Y, Yang H, Wang Z, et al (2013a) Functional TRPV1 expression in human corneal fibroblasts. *Exp. Eye Res.* p. 121-9.
- Yang Y, Yang H, Wang Z, et al (2013b) Wakayama symposium: dependence of corneal epithelial homeostasis on transient receptor potential function. *Ocul Surf* p. 8-11.
- Zhang F, Yang H, Wang Z, et al (2007) Transient receptor potential vanilloid 1 activation induces inflammatory cytokine release in corneal epithelium through MAPK signaling. *J. Cell. Physiol.* p. 730-9.